REMARKS

Claims 1, 7-9, 40, and 42-50 are pending in the instant application. By this amendment, claims 1, 42, 43, and 46 have been amended without prejudice for purposes of clarity, to replace the term "prevention" with "inhibition." Support for the amendment to claims 1, 42, 43, and 46 is found at page 43, lines 26-30.

Therefore, claims 1, 7-9, 40, and 42-50 will be pending upon entry of the instant amendments in the instant application. Applicants respectfully request that the amendments and remarks made herein be entered into the record of the instant application.

1. THE REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, FOR LACK OF ENABLEMENT SHOULD BE WITHDRAWN

Claims 1, 7-9, 40, 42-50 are rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enabling disclosure. In particular, the Examiner contends that the specification does not enable use of the claimed pharmaceutical compositions for the prevention of disease such as cancer or HIV. Applicants submit that the claims are enabled for the reasons set forth below.

Firstly, Applicants point out that claims 7-9, 40, 44, 45, and 47 relate to purified molecular complexes or purified populations of molecular complexes, and do not specify use for prevention of disease. While the subject matter of these claims can be used for prevention of disease, the use of the claimed subject matter, *e.g.*, in treatment, is sufficient to enable the claims. Thus, the rejection of claims 7-9, 40, 44, 45, and 47 for lack of enablement is improper.

With respect to claims 1, 42-43, 46, and 48-50, the Examiner's attention is directed to the opinion of the Court of Appeals for the Federal Circuit (Federal Circuit) in *In re Brana*, 51 F.3d.1560, 34 U.S.P.Q.2d 1437 (Fed. Cir. 1995). In *Brana*, the Board had affirmed a final rejection under Section 112, 1st paragraph, of claims covering certain compounds asserted to be useful as anti-tumor substances because it was alleged that the specification was non-enabling since it did not sufficiently establish that the claimed compounds had a practical utility, *i.e.*, as anti-tumor agents. *Id.* at 1563, 1564.

The Federal Circuit emphatically reversed the Board's decision. First, it explained the legal standard for compliance with the relevant Section 112 requirement, explaining that "unless there is reason to doubt the objective truth of the statements contained [in the specification] which must be relied on for enabling support", a specification's disclosure "must be taken as in compliance with the enabling requirement." *Id.* at 1566

(emphasis in the original). Further, the *Brana* Court made clear that the Patent and Trademark Office has the initial burden of challenging a presumptively correct assertion of utility; evidence must be presented that those of skill in the art would doubt the disclosure. Only then must the applicant provide rebuttal evidence.

The Federal Circuit further reminded the Commissioner that testing for the full safety and effectiveness of a product is more properly left to the Food and Drug Administration and the requirements under the law for obtaining a patent should not be confused with the requirements for obtaining government approval to market a particular drug for consumption. *Id.* at 1567; *see*, *Scott v. Finney*, 34 F.3d 1058, 1063 (Fed. Cir. 1994).

The Federal Circuit also explained that even if one of skill in the art would have questioned the asserted utility, all applicants need do to overcome the rejection is to proffer sufficient evidence to convince one skilled in the art of the asserted utility. *Id.* at 1566, 1567.

In the *Brana* situation, the Court found that the Patent and Trademark Office had not met its initial burden. Further, the Court held that even if the Patent and Trademark Office had met its burden, the evidence proffered was clearly sufficient to meet the statutory requirement. As explained by the Court:

> We hold as we do because it is our firm conviction that one who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to the art, even though it may eventually appear that the compound is without value in the treatment of humans. *Id.* at 1567 [quoting *In re Krimmel*, 292 F.2d 948, 953 (C.C.P.A 1961)].

The Federal Circuit further reminded the Commissioner that:

> If applicants were required to wait until an animal naturally developed this specific tumor before testing the effectiveness of a compound against the tumor *in vivo*, as would be implied from the Commissioner's argument, there would be no effective way to test compounds *in vivo* on a large scale. *Id.* at 1565.

Secondly, Applicants point out that claims 1, 42, 43, and 46 have been amended to replace "prevention" with inhibition. The claims as thus amended are fully enabled by the specification (see page 43, lines 26-30). In accordance with *Brana*, Applicants submit that the experimental data presented in the Srivastava Declaration,

submitted April 5, 2004, using the OVA (B16F10) cancer animal model is sufficient to enable the claimed compositions for the inhibition of disease. In those experiments, mice were administered complexes of α2M and antigenic molecules that display the antigenicity of OVA20 peptide (OVA tumor antigen) (see page 2, paragraph 7 of Declaration) and subsequently challenged with OVA expressing cancer cells. The results presented in page 3, paragraph 9, of the Declaration show that the animals either exhibited a delay in the onset of tumor growth or exhibited no tumors at all. Applicants assert that the observed delay in onset or absence of tumor growth are exemplary of inhibition of cancer. These results demonstrate that one skilled in the art can use complexes of α2M and antigenic molecules that display the antigenicity of an antigen overexpressed in a cancer cell to inhibit disease such as cancer. The results in the OVA animal model described above are sufficient to demonstrate that one skilled in the art would have been able to use the claimed compositions to inhibit disease such as cancer.

In accordance with *Brana*, the results of administering the claimed compositions for inhibition of disease in a animal model (e.g., OVA (B16F10) cancer model) are sufficient to demonstrate that the claimed compositions exhibit some desirable pharmaceutical property and that one skilled in the art can use the claimed compositions to inhibit cancer or tumor or infectious disease.

Applicants submit that the experimental data presented in the Srivastava Declaration using the OVA cancer animal model is correlative to inhibition of cancer in human subjects. In view of the results presented in the Declaration of Srivastava, one of skill in the art would be convinced that complexes of α2M and antigenic molecules that display the antigenicity of a cancer or infectious disease agent can be used to inhibit cancer or infectious disease in a human, and thus can be present in the effective amounts recited in the claims.

The Examiner contends that Byers (1999, CA Cancer J. Clin.49:353-361) stands for the proposition that experimental animal models are not predictive or correlative to human subjects. Byers indicates that randomized controlled trials produce more definitive results than observational studies with respect to causality and that such randomized trials are typically "rare compared with observational studies because they are justified only after considerable evidence has been accumulated from animal, *in vitro*, and observational studies" (see page 358, 1st column, last paragraph). Applicants point out that Byers merely indicates that observational studies are less definitive than randomized studies, but is silent with respect to the correlation of results in animal models to humans. In fact, Byers acknowledges

the common use of animal models to justify further studies in humans, which indicates that there is an accepted correlation between results in animal models and efficacy in humans. Thus, Byers shows that animal models have value in assessing the efficacy of compounds in inhibition of disease that can be extrapolated or correlated to humans.

In accordance with *Brana*, the full testing for safety and effectiveness of a product is more properly left to the Food and Drug Administration. The results of administering the claimed compositions for inhibition of disease in a animal model are sufficient to demonstrate that one skilled in the art can use the claimed compositions. In addition, the results in the OVA animal model described above are sufficiently convincing to demonstrate one skilled in the art that one can use the claimed compositions to inhibit disease such as cancer or HIV.

With respect to inhibition of infectious disease, Applicants submit that one skilled in the art with knowledge of the above data would predict that the claimed compositions can be used to inhibit infectious disease because the mechanism by which an α2M polypeptide noncovalently associated with an antigenic molecule having the antigenicity of an infectious disease antigen stimulates an immune response to inhibit disease is the same as the mechanism by which α2M polypeptide noncovalently associated with an antigenic molecule having the antigenicity of a cancer antigen can be used to inhibit cancer. Both inhibitory therapies use the same common pathway wherein the α2M polypeptide complex stimulates an immune response against the associated antigen. Thus, the results described above in the Srivastava Declaration using the OVA cancer antigen would be sufficiently convincing to one skilled in the art that the claimed compositions comprising an α2M polypeptide noncovalently associated with an antigenic molecule which displays the antigenicity of a antigen overexpressed in a cancer cell or displays the antigenicity of an antigen of an infectious agent can be used to inhibit cancer and infectious disease, respectively.

In view of the forgoing arguments and amendments, Applicants respectfully request the Examiner's withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

2. THE REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, FOR LACK OF WRITTEN DESCRIPTION SHOULD BE WITHDRAWN

The Examiner has maintained the rejection of claims 1, 7-9, 40, and 42-50 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. In particular, the Examiner states that "Neither the claims not the specification

teach any identifiable characteristics that are associated with these 'antigenic molecules which displays the antigenicity' of a tumor or infectious agent" (see Office Action page 6).

Applicant respectfully disagrees and asserts that the specification as filed provides an adequate written description for the claimed compositions. An adequate written description for the claimed compositions does not require that the specification provide a detailed structure of every, or even most, species of the genus of antigenic molecules which display the antigenicity of an antigen overexpressed in a cancer cell or and antigenic molecule which displays the antigenicity of an antigen of an infectious agent, for the reasons set forth below.

The legal standard for the written description requirement of 35 U.S.C. § 112, first paragraph, requires that an applicant "must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention." *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555; 19 U.S.P.Q.2d 1111 (Fed. Cir. 1991). According to the relevant case law, a claimed genus must be supported by a description of relevant identifying characteristics of a representative number of species. *Regents of University of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997), cert. denied 523 U.S. 1089 (1998). What constitutes a "representative number of species" depends upon the knowledge and skill in the art. Moreover, such a description need not be sufficient to provide support to claim each individual species encompassed by the genus. The description is deemed sufficient if it demonstrates to the skilled artisan that the applicant was in possession of the necessary common attributes of the members of the genus. *Eli Lilly*, 119 F.3d at 1568.

The Examiner's attention is directed to the Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112 ¶ 1, "Written Description" Requirement" ("the Guidelines") (published in the January 5, 2001 Federal Register at Volume 66, Number 4, pages 1099-1111). The Guidelines specify that an applicant may show that an invention is complete by "disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention." (*Id.* at page 1106, column 1, lines 22-33). According to the Guidelines, for each claimed genus, the test requires determination of whether there is sufficient description of

> . . .a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, functional characteristics when coupled with known or disclosed correlation between function and structure, or some combination of such identifying characteristics sufficient to show the applicant was in possession of the claimed genus.

Id. at page 1106, col. 3, lines 12-29

According to the Guidelines, there are situations where description of even one species adequately supports a genus. "Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (*Id.* at page 1106, col. 3, lines 42-50). Where the specification discloses any relevant identifying characteristics, i.e., physical, chemical and/or functional characteristics, sufficient to allow a skilled artisan to recognize the applicant was in possession of the claimed invention, a rejection for lack of written description under Section 112, first paragraph, is misplaced.

The instant claims are directed to pharmaceutical compositions, purified molecular complexes, and purified populations of molecular complexes comprising a complex of alpha (2) macroglobulin polypeptide noncovalently associated with an antigenic molecule which displays the antigenicity of an antigen overexpressed in a cancer cell or which displays the antigenicity of an antigen of an infectious agent.

The case law on which the Examiner based his rejection discussed written description requirements in the context of claiming nucleic acids. In particular, at pages 6 and 7 in the Office Action dated November 5, 2003, the Examiner relied on *The Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1568 (Fed. Cir. 1997), cert. denied, 523 U.S. 1089 (1998), wherein the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. Applicant respectfully points out that this holding regarding a genus of nucleic acids is not applicable to the instantly claimed invention. Eli Lilly concerns claims directed to genera of vertebrate and mammalian insulin cDNAs based merely on the disclosure of a single species, rat insulin cDNA, a prophetic method for obtaining another species (human insulin cDNA), and the functional activity of the other species in the claimed genera. Id. The court in Eli Lilly held that a "description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs,...or of a reictation of structural features common to the members of the genus, which features constitute a substantial portion of the genus" [footnote omitted]. *Id.* at 1569.

The antigenic molecules which display the antigenicity of an antigen overexpressed in a cancer cell or which displays the antigenicity of an antigen of an infectious agent of the claims of the instant application have in common the characteristic of (i) antigenicity, and (ii) being associated with an alpha (2) macroglobulin polypeptide.

Because alpha (2) macroglobulins are not limited in binding to a particular structure of antigenic molecule, the claims encompass antigenic molecules that are, in contrast to the nucleic acids of the claims at issue in Eli Lilly, diverse in nature and lack any common structural features other than the presence of an antigenic determinant (epitope). However, antigenic determinants are characterized by diversity; therefore, it is not the description of a common structural feature that gives rise to a written description of the genus, but the identifying characteristic of possessing an epitope. Thus, a written description of such antigenic molecules is more analogous to a written description of antibodies than of the nucleic acids underlying the Eli Lilly decision. In this regard, the Examiner is invited to review the Revised Interim Written Description Guidelines Training Materials, March 1, 2000, available at http://www.uspto.gov/web/offices/pac/writtendesc.pdf (accessed March 17, 2005) ("the Training Materials"). Example 16 on page 59 of the Training Materials analyzes a written description of antibodies and concludes that:

> Considering the routine art-recognized method of making antibodies to fully characterized antigens, the well defined structural characteristics for the five classes of antibody, the functional characteristics of antibody binding, and the fact that the antibody technology is well developed and mature, one of skill in the art would have recognized that the spectrum of antibodies which bind to antigen X were implicitly disclosed as a result of the isolation of antigen X.

Accordingly, the relevant written description inquiry here is whether the functional characteristics of antigenic molecules are sufficiently well-known and the technology sufficiently well-developed to allow a skilled artisan to recognize that such molecules are implicitly disclosed in the specification, thereby placing applicant in possession of the claimed invention.

Antigenic molecules were commonly known in the art, numerous examples of which are provided by the instant specification. For example, tumor-specific or tumor-associated antigens are exemplified in Section 5.2.4.1, at page 37, lines 11-24, page 45, line 29, and page 50, line 31 through page 51, line 7. The specification also provides an example of a peptide sequence of a known murine leukemia virus gp70-derived H2-Ld-restricted peptide AH-1 (see page 59, lines 26-29, where this peptide is disclosed in the context of gp96 chaperoning of peptides, and page 61, lines 12-14). Examples of infectious agents from which antigenic molecules can be prepared are described in the specification at page 37, lines 28-36.

In the instant situation, in addition to the antigenic molecules described in the specification, the literature is rife with teachings of antigenic molecules, *e.g.*, of cancer and

infectious disease. Moreover, assays for identifying and characterizing antigenic determinants were well known in the art at the time of filing the application, and the specification provides numerous such assays that the skilled artisan could use to readily determine the antigenicity of molecules not specifically enumerated in the specification. The specification teaches that "antigenic molecules" can be selected for their antigenicity or their immunogenicity, as determined by immunoassays or by their ability to generate an immune response" (page 37, lines 8-10). In this regard, methods for the determination of immunogenicity of antigenic molecules and complexes of alpha (2) macroglobulin and antigenic molecules are provided in Section 5.3.4, pages 48-49 of the specification. The specification also teaches isolation of antigenic molecules in Section 5.2.4, pages 37-41 of the specification, including isolation of peptides from alpha (2) macroglobulin-peptide complexes (page 39, lines 1-26) and isolation of peptides from MHC-peptide complexes (page 39, line 28 through page 40, line 5). The specification further describes methods known in the art for synthesis of antigenic molecules which can be used for complexing to alpha (2) macroglobulin (page 40, lines 6-30) as well as the use of known tumor-specific antigens or fragments or derivatives thereof (page 37, lines 12-24) and antigenic molecules comprising epitopes of viral (page 37, lines 29-36), bacterial (page 38, lines 1-4), protozoal (page 38, lines 5-9) and parasitic (page 38, lines 9-12) antigens.

Not only was the technology for identifying and characterizing antigenic molecules advanced and predictable at the time of filing the instant application, as discussed above, but so was the technology for producing antigenic molecules and complexes of antigenic molecules and alpha (2) macroglobulin. For example, antigenic molecules can be produced by chemical synthesis or recombinant means, which were well known at the time the present application was effectively filed. Complexes of antigenic molecules and alpha (2) macroglobulin can be generated in vitro (Section 5.2.2 of the specification beginning on page 35), or purified from various sources, including antigenic molecules purified as complexes with alpha (2) macroglobulin (page 33, lines 4-10). The various sources described are tissues, isolated cells, and immortalized eukaryote cell lines infected with a preselected intracellular pathogen, tumor cells or tumor cell lines (page 28, lines 10-12).

Given the maturity of the technology for identifying and producing antigenic molecules and the teachings of the instant specification, Applicant submits that one of skill in the art would consider the entire spectrum of antigenic molecules encompassed by the claimed pharmaceutical compositions, purified molecular complexes, and purified populations of molecular complexes implicitly disclosed in the specification. Accordingly,

Applicant submits that the specification provides an adequate written description of the antigenic molecules of the claimed subject matter given the appropriate standard elucidated above.

In view of the forgoing arguments and amendments, Applicants respectfully request the Examiner's withdrawal of the rejections of claims 1, 7-9, 40, and 42-50 under 35 U.S.C. § 112, first paragraph.

3. THE REJECTION UNDER 35 U.S.C. § 101, AND 35 U.S.C. § 112, FIRST PARAGRAPH, FOR LACK OF UTILITY DESCRIPTION SHOULD BE WITHDRAWN

Claims 1, 7-9, 40, and 42-50 are rejected under 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph, because the claimed invention is allegedly not supported by either a credible asserted utility or a well established utility. The Examiner contends that the present fact pattern is similar to that set forth in Example 2 of the Utility Guidelines.

According to the Utility Guidelines, the standard for a utility rejection is the same whether under § 101 or § 112 (Federal Register 66 (4), at 1097 (January 5, 2001); Section II.A.). "Office personnel should not impose a 35 U.S.C. 112, first paragraph, rejection grounded on a "lack of utility" basis unless a 35 U.S.C. 101 rejection is proper" (M.P.E.P. 2107.IV). An examiner should, in the first instance, defer to the statements regarding utility in the specification as being true, especially when supported by evidence in the record:

> For obvious reasons of efficiency and in deference to an applicant's understanding of his or her invention, when a statement of utility is evaluated, Office personnel should not begin by questioning the truth of the statement of utility. Instead, any inquiry must start by asking if there is any reason to question the truth of the statement of utility. This can be done by simply evaluating the logic of the statements made, taking into consideration any evidence cited by the applicant. If the asserted utility is credible (*i.e.*, believable based on the record or the nature of the invention), a rejection based on "lack of utility" is not appropriate. Clearly, Office personnel should not begin an evaluation of utility by assuming that an asserted utility is likely to be false, based on the technical field of the invention or for other general reasons. (M.P.E.P. 2107.01.A.)

In cases in which pharmacological processes are claimed, such as the present application, animal data is particularly relevant in evaluating utility.

> If reasonably correlated to the particular therapeutic or pharmacological utility, data generated using *in vitro* assays, or from testing in an animal model or a combination thereof almost invariably

will be sufficient to establish therapeutic or pharmacological utility for a compound, composition, or process. (M.P.E.P. 2107.03.III.).

Applicants point out that claims 7-9, 40, 44, 45, and 47 relate to purified molecular complexes or purified populations of molecular complexes, and do not specify use for prevention of disease. While the subject matter of these claims can be used for prevention of disease, the use of the claimed subject matter, *e.g.*, in treatment, is sufficient to meet the utility requirement. The Federal Circuit has determined that to satisfy the utility requirement of a § 101, patent applicant need show utility for only one disclosed purpose. *Raytheon Co. v. Roper Corp.*, 724 F.2d 951, 958., *cert. denied,* 469 U.S. 835 (1984).Thus, the rejection of claims 7-9, 40, 44, 45, and 47 for lack of support of either a credible asserted utility or a well established utility is improper.

Claims 1, 42, 43, and 46 have been amended to replace "prevention" with "inhibition." Applicants submit that the pharmaceutical compositions of claims 1 and 42 have utility for the treatment or inhibition of cancer and that the pharmaceutical compositions of claims 43 and 46 have utility for the treatment or inhibition of infectious disease, for all the reasons discussed above by Applicants in response to the rejection under 35 U.S.C. § 112, for lack of enablement.

In the present instance, Applicants have asserted a specific utility for the claimed compositions, *i.e.*, treatment or inhibition of cancer or infectious disease. The utility asserted by the Applicants is also substantial because treatment or inhibition of cancer and infectious disease clearly define "real world" context of use. The utility asserted by the Applicants is also credible. Thus, the rejection for lack of credible utility is improper.

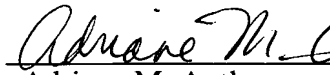
Therefore, Applicants respectfully request the Examiner's withdrawal of the rejections of claims 1, 7-9, 40, and 42-50 under 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph.

CONCLUSION

Entry of the foregoing amendment and remarks into the record of the above-identified application is respectfully requested. Applicants submit that the remarks and amendments made herein now place the claims in condition for allowance. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

Respectfully submitted,

Date: March 23, 2005



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